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EP0868208 (A1)  
BR9702301 (A)  
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Abstract not available for TW389705

Abstract for related application, publication no. WO 97/48483:

## **AFFINITY MEMBRANE SYSTEM AND METHOD OF USING SAME**

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**WO9748483**

**Publication date:**

**1997-12-24**

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**- european:**

**A61M1/36P; B01D61/00; B01D63/02; B01D67/00J18; B01D69/14B; B01J20/28**

**Application number:** **WO1997US10467 19970616**

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EP0868208 (A1)  
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**Cited documents:**

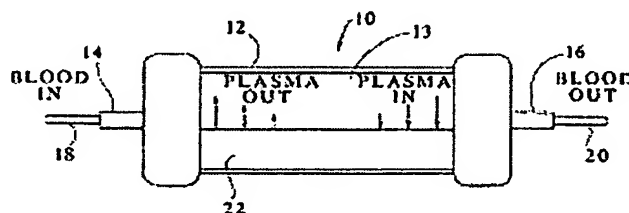


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### **Abstract of WO9748483**

The present invention provides an improved affinity membrane device and method for the effective removal of target molecules in plasma. The affinity membrane device is designed for use in an extracorporeal blood circuit and can be employed concurrently with other therapeutic processes for the purification of blood. The device of the present invention consists of hollow fiber membranes having specified dimensions and transfer properties, ligand immobilized to the pore surface of the hollow fibers, and a housing to encase the hollow fibers and allow appropriate entry and exit of the blood. In a preferred embodiment, specific immobilization chemistries are utilized to attach the ligands to the hollow fibers for optimal function.



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[54]名稱：親和性薄膜系統及使用親和性薄膜系統之方法

[21]申請案號：086108090

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[32]1996/06/20

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[57]申請專利範圍：

1.一種用於選擇性除去包含在血液的血漿中的目標分子之親和性薄膜裝置，其係包括：

一種具有血液從其進入和退出之一入口和一出口之延長罩殼；

裝在該延長罩殼內部空穴之空心纖維，該空心纖維具有將血液分離成血漿和細胞成分之適當細孔大小的細孔，該等空心纖維具有壁厚度約300到3500微米且具有約70到140微米之內徑，細孔具有固定於細孔內表面之配位子，配位子具有對於血漿中的目標分子之親和性，其中該等配位子係固定於具有約50至250個碳原子鏈長的聚乙二醇之細孔的表面上，

其中血液之細胞成分不流進空心纖維的細孔內，且血漿藉由空心纖維內跨膜壓力所產生的正向過濾而輸入細孔內，該正向過濾係在外部泵不存在下發生，以產生血漿橫流過該等空心纖維。

2.根據申請專利範圍第1項之裝置，其中細孔大小約0.2到0.6微米之範圍。

3.根據申請專利範圍第1項之裝置，其中該等空心纖維具有用於固定配位子以允許目標分子之充份結合的適當表面面積的壁厚度。

4.根據申請專利範圍第1項之裝置，其中該等空心纖維係由選自下列所組成族群中的材料所製得：纖維素三乙酸酯；聚矽；聚丙烯腈；乙烯／乙烯醇共聚物；聚甲基甲基丙烯酸酯；聚醯胺；聚丙烯；纖維素乙酸酯；再生纖維素；聚碳酸酯；聚乙烯；聚乙烯醇；和聚氯乙稀。

5.根據申請專利範圍第1項之裝置，其中該等配位子固定於具有抗生物素蛋白／生物素分子複合物的細孔表面。

6.根據申請專利範圍第1項之裝置，其中該等配位子為修飾目標分子和一旦他們被修飾時釋放目標分子的酵素。

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- 7.根據申請專利範圍第1項之裝置，其中該延長罩殼具有單一出口和單一入口。
- 8.根據申請專利範圍第1項之裝置，進一步包括連接到延長罩殼之血漿導管，其允許利用已存在的壓力梯度將血漿的非目標分子與該等細胞成分再結合。
- 9.一種選擇性除去存在於血漿中的目標分子之方法，其包括下列步驟：  
提供空心纖維膜裝置，該裝置具有(a)一具有血液從其進入和退出之單一入口和單一出口之延長罩殼；和(b)包在罩殼內側之空心纖維，該空心纖維具有用於將血液分離成血漿和細胞成分之適當細孔大小的細孔，該等空心纖維具有壁厚度約300到3500微米且具有約70至140微米之內徑，該等細孔具有結合至具約50至250碳原子鏈長的聚乙二醇之細孔內表面之配位子，該等配位子具有對於血漿中的目標分子之親和性；  
將血液輸送至罩殼入口內；  
藉由靠近入口處跨膜壓力所產生的正向過濾使血液的血漿流進該等空心纖維之細孔內，同時不允許該等細胞成分流至其中；  
將該等配位子和血漿中的目標分子接觸，經臨床意義上的時間以允許目標分子結合到該等配位子；和  
使血漿的非目標分子藉由靠近目標分子處負跨膜壓力所產生的反向過濾而經空心纖維的細孔流回，以和血液之細胞成分再結合。
- 10.根據申請專利範圍第9項之方法，其進一步包括藉由已存在的壓力梯度經由血漿導管使非目標分子和該等細胞成分再結合。
- 11.根據申請專利範圍第9項之方法，其中該等空心纖維中的細孔大小於約0.2到0.6微米之範圍。
- 12.根據申請專利範圍第9項之方法，其中該等空心纖維係由選自下列所組成族

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- 群中的材料所製得：纖維素三乙酸酯；聚醚；聚丙烯腈；乙烯／乙烯醇共聚物；聚甲基甲基丙烯酸酯；聚醯胺；聚丙烯酸；纖維素乙酸酯；再生纖維素；聚碳酸酯，聚乙烯；聚乙醇醇；和聚氧乙烯。
- 13.一種用於選擇性除去包含在血液的血漿中的目標分子之親和性薄膜裝置，其係包括：  
一種具有血液從其進入和退出之一入口和一出口之延長罩殼；  
裝在該延長罩殼內部空穴之單束空心纖維，該空心纖維具有將血液分離成血漿和細胞成分之適當細孔大小的細孔，細孔具有固定於具約50至250個碳原子鏈長的聚乙二醇之細孔內表面之配位子，配位子具有對於血漿中的目標分子之親和性，其中該等空心纖維具有壁厚度約300至3500微米且具有約70至140微米之內徑，其中血液之細胞成分不流進空心纖維的細孔內，且血漿藉由空心纖維內跨膜壓力所產生的正向過濾而輸入細孔內，該正向過濾係在外部泵不存在下發生，以產生血漿橫流過等空心纖維。
- 14.一種空心纖維膜，其包含：  
多數之延長空心纖維，各纖維具有圍住內腔週邊壁，週邊壁具有多數延伸其上之細孔，細孔的數目和組態有效將血液分離成血漿和細胞成分，各細孔具有結合至細孔內表面之配位子和具有致使提供附著配位子的適當表面面積之長度尺寸，以確定該等配位子捕捉實質上所有的目標分子，該週邊壁具有厚度約300到3500微米及該等空心纖維具有約70到140微米之內徑，且其中該等配位子固定於具有約50到250個碳原子鏈長的聚乙二醇之細孔表面。
- 15.根據申請專利範圍第14項的空心纖維膜，其中該等空心纖維係由選自下列所組成族群中的材料所製得：纖維素三乙

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酸酯；聚醚；聚丙烯腈；乙烯／乙烯醇共聚物；聚甲基甲基丙烯酸酯；聚醚胺；聚丙稀；纖維素乙酸酯；再生纖維素；聚碳酸酯，聚乙烯；聚乙醇醇；和聚氯乙烯。

16.根據申請專利範圍第14項的空心纖維膜，其中該配位子係結合至具有抗生物素蛋白／生物素分子複合物的細孔。

17.根據申請專利範圍第14項的空心纖維膜，其中多數之延長空心纖維係以一單束存在。

18.一種減少罹患以過量含量的目標溶質為特徵的醫療情況之病人中的目標溶質之方法，其係包括：

將全血從病人移出；

提供空心纖維膜裝置，該裝置具有(a)一具有血液從其進入和退出之單一入口和單一出口之延長罩殼；和(b)裝在罩殼內側之空心纖維，空心纖維具有多數延經其上之細孔，細孔的數目和組態有效將血液分離成血漿和細胞成分，該等細孔具有結合至細孔內表面之配位子，該等配位子具有對於血漿中的目標溶質之親和性，該等配位子固定於具有約50至250個碳原子鏈長的聚乙二醇之細孔的內表面上；

將血液輸送至罩殼入口內；

藉由靠近入口處跨膜壓力所產生的正向過濾使血液的血漿流進該等空心纖維之細孔內，同時不允許該等細胞成分流至其中；

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將配位子與血漿中的目標溶質接觸經臨床意義上的時間，以實質上降低來自血漿的目標溶質的濃度含量；

使血漿的非目標溶質藉由靠近入口處負跨膜壓力所產生反向過濾而經空心纖維的細孔流回，以使非目標溶質與血液之細胞成分再結合以形成一經處理的血液產物，以及

將經處理的血液產物灌注至病人內。

5. 19.根據申請專利範圍第18項之方法，其中該配位子為多細胞系抗體。

20.根據申請專利範圍第18項之方法，其中該配位子為一種可結合自身抗體的自身抗原。

15. 21.根據申請專利範圍第18項之方法，其中該配位子為一種酵素。

圖式簡單說明：

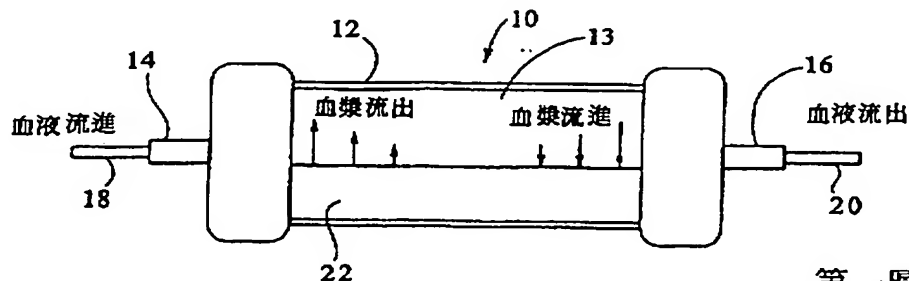
第一圖為一個本發明的親和性薄膜裝置之具體實施例的平面圖。

20. 第二圖為另一個本發明的親和性薄膜裝置之具體實施例的平面圖。

第三圖為說明藉由發生在親和性裝置的內孔穴中的正向和反向過濾血漿流過纖維壁的單一空心纖維之概要放大表示法。

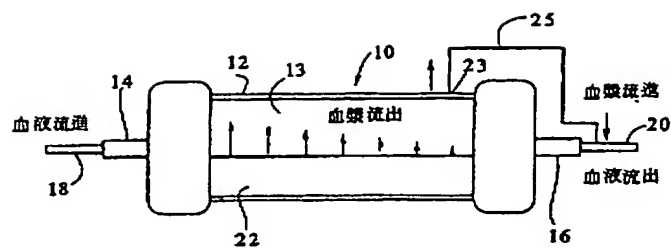
25. 第四圖為說明血漿流經纖維壁中細孔和結合至固定配子目標分子之單一纖維壁的空心纖維之概要放大表示法。

30. 第五圖一般說明本發明的生物素－抗生物素蛋白固定圖式。

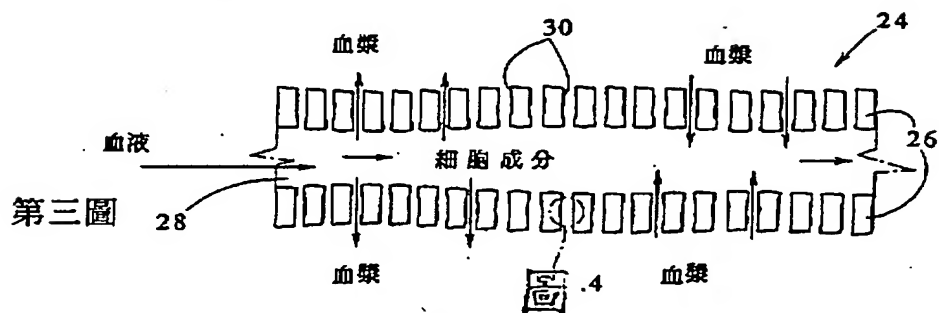


第一圖

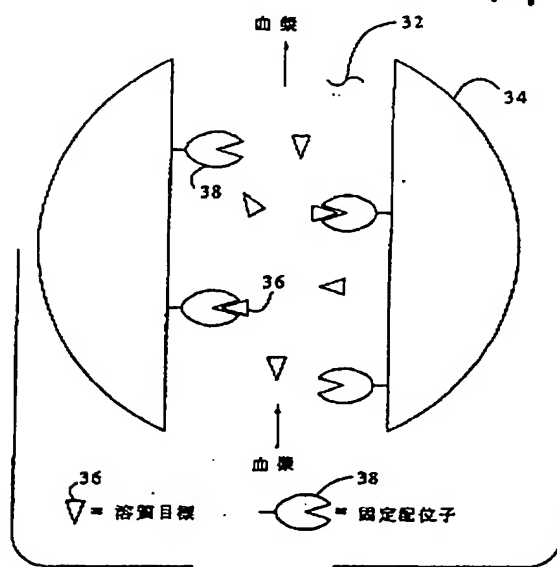
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第二圖

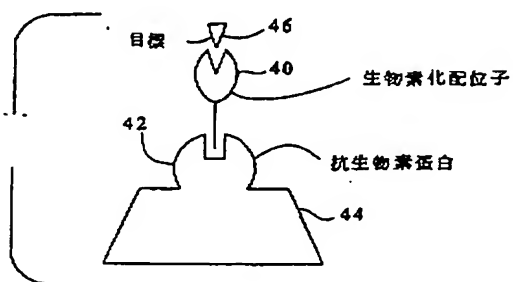


第三圖



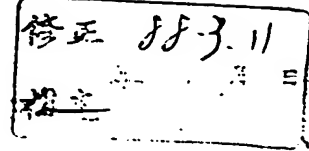
第四圖

第五圖



公告本

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WE CLAIM:

1. An affinity membrane device utilized for the selective removal of targeted molecules contained in plasma of blood comprising:

5 an elongated housing having an inlet port and an outlet port for entry and exit of blood therefrom;

hollow fibers encased in an internal cavity of the elongated housing, the hollow fibers having pores with suitable pores sizes for separating blood into plasma and cellular components, the hollow fibers having wall thicknesses of about 300 to 3500 microns and having internal diameter of about 70 to 140 microns, the pores having ligands immobilized to an internal surface of the pores, the ligands having an affinity for the targeted molecules in the plasma, wherein the ligands are immobilized to the surface of the pores with polyethylene glycol having a chain length of about 50 to 250 carbon atoms,

wherein the cellular components of the blood do not flow into the pores of the hollow fibers and the plasma is transported into the pores by means of positive filtration created by transmembrane pressures within the hollow fibers, the positive filtration occurring in the absence of an external pump for generating plasma flow across the hollow fibers.

25 2. The device of Claim 1 wherein the pore sizes range from approximately 0.2 to 0.6 microns.

3. The device of Claim 1 wherein the hollow fibers have wall thicknesses with adequate surface area for attachment of the ligands to allow for the sufficient binding of the targeted molecules.

煩請委員明示，本係是否變更原實質內容

4. The device of Claim 1 wherein the hollow fibers are made of material selected from the group consisting of: cellulose triacetate; polysulfone, polyacrylonitrile; ethylene/vinyl alcohol copolymer; polymethylmethacrylate; 5 polyamide; polypropylene; cellulose acetate; regenerated cellulose; polycarbonate, polyethylene; polyvinylalcohol; and polyvinylchloride.

5. The device of Claim 1 wherein the ligands are immobilized to the surface of the pores with an 10 avidin/biotin molecular complex.

6. The device of Claim 1 wherein the ligands are enzymes that modify the targeted molecules and release the targeted molecules once they are modified.

7. The device of Claim 1 wherein the elongated 15 housing has a single outlet port and a single inlet port.

8. The device of Claim 1 further comprising a plasma conduit attached to the elongated housing that allows non-targeted molecules of the plasma to reunite with the cellular components by means of an existing pressure 20 gradient.

9. A method for the selective removal of target molecules present in plasma comprising the steps of:

providing a hollow fiber membrane device having (a) an elongated housing with a single inlet port and a single 25 outlet port for entry and exit of blood therefrom; and (b) hollow fibers encased inside the housing, the hollow fibers having pores with suitable pores sizes for separating blood into plasma and cellular components, the hollow fibers having wall thicknesses of about 300 to 3500 microns and having internal diameter of about 70 to 140 microns, the pores having

ligands immobilized to an internal surface of the pores with polyethylene glycol having a chain length of about 50 to 250 carbon atoms, the ligands having an affinity for the targeted molecules in plasma;

5            transporting blood into the inlet port of the housing;  
             causing the plasma of the blood to flow into the pores  
             of the hollow fibers by means of positive filtration created  
             by a positive transmembrane pressures near the inlet port  
             while not allowing the cellular components to flow into the  
10           same;

             contacting the targeted molecules in the plasma with  
             the ligands for a clinically significant period of time to  
             allow for the binding of the targeted molecules to the ligands;  
             and

15           causing non-targeted molecules of the plasma to flow  
             back through the pores of the hollow fibers by means of  
             reverse filtration created by a negative transmembrane  
             pressure near the outlet port to reunite the non-targeted  
             molecules with the cellular components of the blood.

20           10. The method of Claim 9 further comprising causing  
             the non-targeted molecules to reunite with the cellular  
             components via a plasma conduit by means of an existing  
             pressure gradient.

25           11. The method of Claim 9 wherein the pore sizes in  
             the hollow fibers range from approximately 0.2 to 0.6  
             microns.

             12. The method of Claim 9 wherein the hollow fibers  
             are made of material selected from the group consisting of:  
             cellulose triacetate; polysulfone; polyacrylonitrile;  
             ethylene/vinyl alcohol copolymer; polymethylmethacrylate;



polyamide; polypropylene; cellulose acetate; regenerated cellulose; polycarbonate, polyethylene; polyvinylalcohol; and polyvinylchloride.

5        13. An affinity membrane device utilized for the selective removal of targeted molecules contained in plasma of blood comprising:

      an elongated housing having an inlet port and an outlet port for entry and exit of blood therefrom;

10        a single bundle of hollow fibers encased in an internal cavity of the elongated housing, the hollow fibers having pores with suitable pores sizes for separating blood into plasma and cellular components, the pores having ligands immobilized to an internal surface of the pores with polyethylene glycol having a chain length of about 50 to 250  
15        carbon atoms, the ligands having an affinity for the targeted molecules in the plasma, the hollow fibers having wall thicknesses of about 300 to 3500 microns and having internal diameter of about 70 to 140 microns,

20        wherein the cellular components of the blood do not flow into the pores of the hollow fibers and the plasma is transported into the pores by means of positive filtration created by transmembrane pressures across the membrane, in the absence of an external pump for generating plasma flow across the hollow fibers.

25        14. A hollow fiber membrane comprising:

      a plurality of elongated hollow fibers, each fiber having a peripheral wall surrounding a lumen, the peripheral wall having a plurality of pores extending therethrough, the number and configuration of the pores being effective to separate blood into plasma and cellular

components, each pore having ligand bound to an internal surface and having a length dimension such that adequate surface area is provided for the attachment of the ligand to ensure that the ligands capture substantially all target molecules, the peripheral wall having a thickness ranging from approximately ranging from approximately 300 to 3500  
5 microns, and the hollow fibers having internal diameter of approximately 70 to 140 microns, and wherein the ligands are immobilized to the surface of the pores with polyethylene glycol having a chain length of about 50 to 250 carbon atoms

15. The hollow fiber membrane of Claim 14 wherein the  
10 hollow fibers are made of material selected from the group consisting of: cellulose triacetate; polysulfone; polyacrylonitrile; ethylene/vinyl alcohol copolymer; polymethylmethacrylate; polyamide; polypropylene; cellulose acetate; regenerated cellulose; polycarbonate,  
15 polyethylene; polyvinylalcohol; and polyvinylchloride.

16. The hollow fiber membrane of claim 14 wherein the ligands are also bound to the pores with an avidin/biotin molecular complex.

17. The hollow fiber membrane of claim 14, wherein the  
20 plurality of elongated hollow fibers are in a single bundle.

18. A method for reducing concentration levels of a target solute in a patient suffering from a medical condition characterized by excessive levels of the target  
25 solute comprising:

removing whole blood from the patient;

providing a hollow fiber membrane device having (a) an elongated housing with a single inlet port and a single outlet port for entry and exit of blood therefrom; and (b) hollow fibers encased inside the housing, the hollow fibers

having a plurality of pores extending therethrough, the number and configuration of the pores effective to separate blood into plasma and cellular components, the pores having ligands bound to an internal surface of the pores, the  
5       ligands having an affinity for the target solute in the plasma, the ligand being immobilized to the internal surface of the pores with polyethylene glycol having a chain length of about 50 to 250 carbon atoms;

          transporting blood into the inlet port of the hous       :  
10       causing the plasma of the blood to flow into the pores of the hollow fibers by means of positive filtration created by a positive transmembrane pressures near the inlet port while not allowing the cellular components to flow into the same;

15       contacting the target solute in the plasma with the ligands for a clinically significant period of time to substantially lower the concentration level of the target solute from the plasma;

          causing non-targeted solute of the plasma to flow back through the pores of the hollow fibers by means of reverse filtration created by a negative transmembrane pressure near the outlet port to reunite the non-targeted solute with .e cellular components of the blood to form a treated blood product; and

          infusing the treated blood product into the patient.

19. The method of Claim 18 wherein the ligand is a polyclonal antibody.

20. The method of Claim 18 wherein the ligand is an autoantigen capable of binding autoantibodies.

21. The method of Claim 18 wherein the ligand is an enzyme.